REMARKS

Claims 1, 2, 4 and 6-23 are pending in the application. In response to the Final Office Action sent on July 23, 2009, Applicants have amended the claims as follows. Claim 1 has been amended to clarify that the adjuvant comprises dimethyldioctadecylammonium-bromide, -chlrodie, -phosphate, or –acetate (DDA). Support for the amendment to Claim 1 can be found throughout the specification and in the claims as originally filed. For example, support for the amendment to Claim 1 can be found in paragraphs **[0017]** and **[0018]** of the specification. Claims 4, 8, and 10 have been cancelled. New Claims 24 and 25 have been added. Support for the new claims can be found throughout the specification and in the original claims as filed. Applicants submit that new Claims 24 and 25 are fully enabled by the specification and note, in particular, the ample support in the working examples for these claims. Examples 1 and 2 of the specification describe the generation of an immunogenic composition comprising, *intra alia*,. DDA and an apolar fraction of a total lipid extract of a mycobacterium, wherein the composition comprises an antigenic component having an antigenic epitope. The efficacy of such an immunogenic composition is illustrated in Table 1 of the specification (between paragraphs **[0098]** and **[0099]**. Paragraphs **[0114]** through **[0119]** describe dose response rates of immunogenic compositions comprising DDA and an apolar fraction or part of the apolar fraction of a total lipid extract of mycobacterium. Paragraphs **[0122]** through **[0125]** set forth the immunological properties of an immunogenic composition as is claimed in new Claims 24-25. Applicants submit that no new matter has been added by these amendments. Thus, Claims 1,-2, 6-7, 9, and 11-25 are presented for examination.

Rejections of Claims 8 and 10 under 35 USC § 112 first paragraph

The Examiner has rejected Claims 8 and 10 under 35 U.S.C. § 112 first paragraph for failing to comply with the enablement requirement. The Examiner asserts that the specification allegedly is not enabled for any vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy or an autoimmune disease wherein the improvement comprises the adjuvant. Claims 8 and 10 have been cancelled, thereby obviating the rejection.

Rejection of Claims 18-19 and 20-23 under 35 U.S.C. § 112, first paragraph

Claims 18-19 and 20-23 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants disagree.

Claims 18-19 are drawn to an immunogenic composition comprising an adjuvant and a tuberculosis antigen. The term "immunogenic" is defined in the specification at paragraph **[0043].** Immunogenicity is well appreciated in the art to be a term referring to a measure of a composition's ability to elicit an immune response. Paragraph **[0123]**, for example, as well as Table 7 of the specification, describe the immunogenicity of various polar, apolar, and total lipid extracts. Support for the adjuvant and a lipid extract of tuberculosis can be found at paragraph **[0014]** of the specification. Claim 18 further recites that the adjuvant comprises a solution *prepared from an evaporated mixture of DDA, DODA, or Dc Chol* (emphasis added). Paragraph **[0055]** of the specification describes in detail the feature of evaporating a mixture of the claimed DDA, DODA, or Dc Chol. The last phrase of Claim 18 includes "an apolar fraction of a total lipid extract of BCG, *M. microti*, *M. tuberculosis, M. vaccae, M. bovis* or *M. africanum* and a solvent." Applicants have described in great detail apolar fractions of a total lipid extract of BCG, *M. microti*, *M. tuberculosis, M. vaccae, M. bovis* or *M. africanum* and a solvent. Paragraph **[0016]** introduces the phrase "apolar fraction or parts of the apolar fraction of the total lipid extract of a mycobacterium." Paragraph **[0025]** describes the adjuvant activity of the lipid fractions. Paragraphs **[0020]** and **[0038]** set forth an exemplary listing of virulent mycobacterium. Claim 19 further clarifies that the tuberculosis antigen in Claim 18 further comprises an ESAT6-Ag85B hybrid or fragment thereof. Applicants draw the PTO's attention to paragraphs **[0028]** and **[0029]**, for example, for support for this additional recitation.

With regard to Claims 20-23, Applicants further urge that the claims are fully supported by the specification and claims as originally filed and do not represent new matter under 35 U.S.C. §112, first paragraph. Claim 20 recites "an adjuvant *consisting essentially of* a resuspension of an evaporated mixture of a solvent, a surfactant selected from the group

consisting of DDA, DODA, and DC CHol and an apolar fraction of a total lipid extract of BCG, *M. microti, M. tuberculosis, M. vaccae, M. bovis,* or *M. africanum.*" Most of the claim components have been described above with reference to Claims 18 and 19. Claim 20, and the claims depending therefrom, differ from the previously discussed claims at least because they include the transitional phrase "consisting essentially of." The transitional phrase "consisting essentially of" has a well-established meaning. According to M.P.E.P. 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified material or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention (emphasis in original). *In re Herz,* 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Just as with other transitional phrases, "consisting essentially of" has a legally-recognized meaning and needs no definition. In Section 2111.03, the M.P.E.P. delivers a distinct and concrete definition of the meaning of the term 'consisting essentially of'. There is no requirement in any section of the M.P.E.P. for the Applicants to define what is meant by this term. Applicants have ample support for the transitional phrase "comprising" which inherently encompasses and includes the transitional phrase "consisting essentially of."

In view of the foregoing, Applicants submit that Claims 18-19 and 20-23 fully comply with the written description requirement under 35 U.S.C. §112, first paragraph and accordingly, Applicants respectfully request withdrawal of the new matter rejections.

Claim Rejections under 35 USC § 102

Claims 1, 4, 6-7, 10-11 and 13 have been rejected under 35 USC § 102 (b) as being anticipated by Liu et al. (U.S. Patent Application Publication No. 20020044951). The Examiner argues that Liu et al. anticipates Claims 1, 4, 6-7, 10-11 and 13 because the reference teaches an adjuvant comprising DOTAP and an apolar fraction or part of a total lipid extract of a mycobacterium. Under 35 U.S.C. § 102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants submit that the Liu et al. reference does not anticipate Claims 1, 4, 6-7, 10-11 and 13, as amended, because it fails to teach each and every element of the claimed invention.

Claim 1 has been amended to clarify that the adjuvant comprises dimethyldioctadecylammonium-bromide, -chloride, -phosphate, or –acetate (DDA) or an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium. Liu et al. is silent with regard to DDA and instead, mentions only DOTAP. Since Claim 1 and the claims depending therefrom recite DDA rather than DOTAP, Liu cannot anticipate the amended claims and Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §102.

Claim Rejections under 35 U.S.C. § 103(a)

The rejection of Claims 1, 4, 6-11, 13 and 15 under 35 USC § 103(a) have been maintained as being obvious in light of Liu and Andersen et al. (U.S. Patent Application Publication No. 20020176867) and Claims 1, 2 and 4 have further been rejected under 35 U.S.C. § 103(a) as being obvious in light of Liu et al. and Ravindranath et al. (U.S. Patent No. 6,218,166). Claims 18-23 have been newly rejected under 35 U.S.C. § 103(a) as being unpatentable in light of Liu et al. in view of Andersen et al. (1994 Vol. 62 No. 6, pgs 2536-2544), Andersen et al. U.S. Patent Appl. No. 20020176867, and Lowrie et al. U.S. patent Appl. No. 20020198168. Applicants reiterate that Liu et al. do not teach an adjuvant "comprising" an apolar fraction or part of a total lipid extract of a mycobacterium and one of skill in the art would not combine either Andersen et al or Ravindranath et al. with Liu et al., because these references teach away from the combination and/or would not provide one of skill in the art with the requisite reasonable expectation of success at arriving at each and every limitation of the claims. Applicants further urge that even if the PTO was to establish a case of *prima facie* obviousness, Applicants have demonstrated unexpected benefits of their claimed composition and these surprising features are non-obvious in view of the art cited by the PTO.

Turning specifically to the Office Action, the Examiner argues that Liu et al. anticipates and/or renders obvious Claims 1, 4, 6-7, 10-11 and 13 because the reference teaches an adjuvant comprising DOTAP and an apolar fraction or part of a total lipid extract of a mycobacterium. Applicants note that Claim 1 has been amended to replace the phrase "a cationic surfactant" with DDA. As discussed above with reference to the § 102 rejection, Liu et al. neither teaches nor suggests DDA. The Examiner argues that Liu et al. and Anderson et al. make Claims 1, 4, 6-11, 13 and 15 obvious because one would incorporate the ESAT-6 and Ag85B antigens taught by Andersen et al. into the adjuvant taught by Liu et al. The Examiner further argues that Liu et al.

and Ravindranath et al. makes Claims 1, 2, and 4 obvious because one would incorporate the phenolic glycolipids taught by Ravindranath et al into the adjuvant taught by Liu et al. Finally, the Examiner asserts that Claims 18-23 are obvious in light of Liu et al. in view of Andersen et al. (1994 Vol. 62 No. 6, pgs 2536-2544), Andersen et al. U.S. Patent Appl. No. 20020176867, and Lowrie et al. U.S. Patent Appl. No. 20020198168. More particularly, the Examiner urges that it would have been obvious to modify the composition to incorporate DDA, whereby the solution prepared was evaporated into a composition in order to take advantage of an effective vaccine against *Mycobacterium tuberculosis*. See Office Action at Page 18. Applicants have previously argued that the art cited by the PTO fails to establish a case of *prima facie* obviousness because the references teach away from the claimed combination of surfactant and apolar fraction or part of a total lipid extract and/or fail to provide one of skill in the art with the requisite reasonable expectation of success at arriving at each and every limitation of the claim. Applicants now further submit that the claims, as amended, are patentably non-obvious over the art cited by the PTO for at least the following additional reasons.

It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, the Applicant need not present arguments or evidence of non-obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams,* a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

Instead, the Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

Applicants respectfully submit that the pending claims as amended are not obvious under 35 U.S.C. § 103(a) for the reasons detailed below.

A review of Liu et al. makes clear that DDA as a cationic surfactant in combination with an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium was neither contemplated nor described by Liu et al. Paragraph [0031] of Liu et al. discloses that the non-peptide antigens may be selected from nonpolar, intermediate and high polarity classes" and a cationic surfactant DOTAP. Cl is disclosed in paragraph [0049] as part of a laundry list of different surfactants which may be used. The specific combination of an apolar fraction or part thereof and DOTAP.CL is not disclosed nor suggested by Liu et al. Moreover, there is no hint or suggestion in the prior art about any difference between the ability of the various lipid fractions from mycobacterium or of the different cationic surfactants to stimulte IFN-γ release, which is indicative of the Th1 response, and a hallmark of adjuvant activity.

Under 35 U.S.C. §103, prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.* 800 F.2d 1091 (Fed. Cir. 1986). The additional art cited by the PTO fails to cure the deficiencies of Liu in estabilishing a *prima facie* case of obviousness under 35 U.S.C. §103(a). Andersen 1994 (Infection and Immunity, vol. 62, no. 6) relates to vaccination of mice against *Mycobacterium tuberculosis* infection with a soluble mixture of secreted mycobaterial proteins. DDA is mentioned as an adjuvant but Andersen is silent with regard to an adjuvant comprising the apolar

lipids. Andersen et al. 2002 (US 2002/0176867) relates to fusion proteins of the immunodominant antigens ESAT6 and Ag85B and discloses a number of different adjuvants which may be used in making vaccines. While Andersen describes various antigenic components, the inventors seek to develop potent single antigen vaccines (*see paragraph 0010),* specifically, the Ag85B-ESAT-6 fusion protein. Andersen et al. states that the 'in addition to being more cost-effective and less time consuming, the delivery of these selected molecules as a single fusion protein has the potential advantage of inducing amplified responses to molecules with a low inherent immunogenicity." (*see paragraph 0016).* Accordingly, Andersen et al. teaches away from adding the ESAT-6 and Ag85B antigens into the milieu of antigens present in extracts as taught by Liu et al so as to arrive at the claimed invention. Moreover, Andersen et al. 2002 is silent with regard to adjuvants comprising apolar lipids.

Applicants assert that the specific combination of the apolar lipids and DDA claimed in the present invention is not disclosed in the prior art. Ravindranath et al., teaches away from applying the harsh conditions (i.e., sonication, vortexing, and extrusion) employed by Liu et al. or the evaporation approach used by the applicants to arrive at the claimed invention. To summarize, Ravindranath et al. describes incorporating an adjuvant into or onto an intact cell. *(see column 3, lines 28-32*) and asserts that the use of whole cells is an *important* feature of the invention so as to insure that the antigens are presented in their natural environments. Ravindranath further urges that any extraction method that removes the antigen from the membrane is likely to alter its immunogenic properties (*see column 4, lines 13-24).* In light of the fact that Anderson et al teaches away from applying a plurality of antigens in a vaccine formulation and Ravindranath et al. teach way from using approaches likely to disrupt the natural presentation of the antigen, as employed by Liu et al., Applicants respectfully submit that Liu et al. in combination with Anderson et al. and/or Ravindranath et al. do not render the claimed invention obvious.

Even if a *prima facie* showing of obviousness were established, the unexpected and surprising effectiveness of the claimed adjuvant comprising DDA and an apolar fraction or part of the apolar fraction of a total lipid extract of mycobacterium in producing a high IFN-γ release would rebut such a showing. Applicants direct the PTO's attention to the fact that the present invention is based, in part, on the finding that the apolar fraction or part thereof of the total lipid

extract from a mycobacterium together with DDA results in a higher release of IFN-γ than a total lipid extract or a polar lipid extract from a mycobacterium together with DDA, a hallmark of adjuvant activity. See, e.g. Table 7 of the specification. Figure 9 of the application shows that total lipids/DDA results in a higher release of IFN-γ than total lipids with other cationic surfactants DTAP and DC-Chol (See also page 27, lines 23-24 of the published PCT Application). Finally, Tables 6 and 6A illustrate that the ability of an adjuvant containing total lipids/DDA to enhance the immune response is not confined to the ESAT6-Ag85B antigen only as similar results are obtained with other antigens, such as MOMP and tetanus toxoid.

The specific combination of apolar lipids and DDA results in an adjuvant capable of producing a high IFN-γ release. This particular combination of lipids and cationic surfactant is neither taught nor suggested in the prior art cited. By contrast, Applicants have discovered that a unique combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a synergistic immune response; this response is both surprising and unexpected. Table 1 of the specification evidences that Ag85B-ESAT6 alone or combined with Ag85B-ESAT6/DDA is not capable of providing any notable protection against *M. tuberculosis*. In contrast, administration of a combination of Ag85B-ESAT6/DDA/apolar fraction of the total lipid extract of a mycobacterium produces a synergistic immune response against *M. tuberculosis*. Similar results were also obtained when using the total lipid extract or the polar fraction of the total lipid extract; however, the immune response obtained when using the total lipid extract or the polar fraction was different from that obtained with the apolar fraction. The apolar fraction produced a much higher IFN-γ response compared to that obtained when using the total lipid extract or the polar fraction. *(see* Table 7) and all of the extracts produced antibodies *(see* Table 8). Quite unexpectedly, Applicants found that the combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a potent adjuvant that can potentiate the immune response to a co-administered antigen.

With regard to the new rejections of Claims 18-23 as unpatentable under 35 U.S.C. § 103(a), the PTO still cites to Liu et al. as the primary reference and further reference Andersen et al. for concluding that the claims are allegedly obvious. Applicants have addressed Liu et al. and Andersen above. Lowrie fails to remedy the deficiencies in the primary references in order to establish *prima facie* obviousness as Lowrie merely teaches that nucleic acid constructs can be

administered as a pharmaceutical formulation. For the same reasons set forth above, Claims 18-23 are patentably non-obvious over the cited art and Applicants respectfully request that the rejections under 35 USC §103 be withdrawn.

Applicants have demonstrated that the cited references fail to provide the necessary teaching, motivation, or suggestion to create a *prima facie* showing of obviousness. Moreover, even if there were a *prima facie* showing of obviousness, such a showing would be rebutted by the significant unexpected advantages provided by the claimed invention. Accordingly, Applicants respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. §103.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

In view of the foregoing, Applicants submit that the application is in condition for allowance. If however, the Examiner believes that any additional issue remains or requires clarification, the Examiner is respectfully requested to call the agent of record in order to more expeditiously advance the examination of this application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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